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Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF  
CORRECTION UNDER 37 CFR 1.322  
Docket No. ARS.102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Claudio Soto-Jara, Claudia Pena-Rossi  
Issued : July 20, 2010  
Patent No. : 7,758,852  
Conf. No. : 4494  
For : OX40R Binding Agents

Mail Stop Certificate of Corrections Branch  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION  
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

**Patent Reads:**

Column 2, line 19:

“CD4 T cells”

Column 29, line 51:

“a SEQ ID NO: 6;”

**Application Reads:**

Page 3, line 7:

--CD4<sup>+</sup> T cells--

Amendment dated April 14, 2009 (original claim 111, renumbered as claim 16, subpart a):

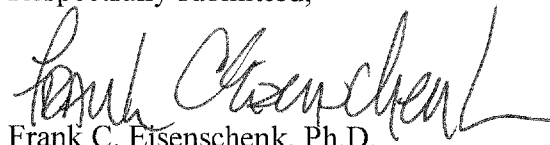
--a) SEQ ID NO: 6; --

<u>Column 29, line 53:</u>	<u>Amendment dated April 14, 2009 (original claim 111, renumbered as claim 16, subpart b):</u>
“deleted said”	--deleted, said--
<u>Column 30, line 10:</u>	<u>Amendment dated April 14, 2009 (original claim 111, renumbered as claim 16, subpart f, iv):</u>
“iv SEQ ID NO:”	--iv) SEQ ID NO: --
<u>Column 30, line 40:</u>	<u>Amendment dated October 29, 2009 (original claim 120, renumbered as claim 25, lines 1-2):</u>
“frision polypeptide”	--fusion polypeptide--.

A true and correct copy of page 3 of the specification as filed and the Amendments dated April 14, 2009 and October 29, 2009 which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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Attachments: Copy of page 3 of the specification  
Amendment dated April 14, 2009  
Amendment dated October 29, 2009

Cumulatively, these expression and functional data raise the possibility that the signal transduction pathways regulated by OX40L-OX40R interactions may help to prolong antigen-specific proliferative responses or otherwise influence the persistence, differentiation or reactivation of effector / memory T cell populations.

5       The interest on OX40R-OX40L system is related to the fact that, even if the intracellular signaling mechanisms have not yet completely understood, the expression profile of OX40R makes this protein a peculiar target for CD4<sup>+</sup> T cells mediated diseases in clinical settings, for example in multiple sclerosis, where it is necessary to delete auto-reactive T cells. The hypothesis is that the products modulating OX40R  
10 activity may not have the serious side effects of conventional immunosuppressive therapies for autoimmune diseases and transplant rejection, which target all T cells.

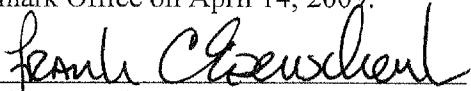
The therapeutic potential of modulating the interaction between OX40L and OX40R was recognized by *in vivo* generated results obtained with OX40L-targeted immunotoxins (Weinberg A et al., 1996), anti-OX40R antibodies (Bansal-Pakala P et  
15 al., 2001), anti-OX40L antibodies (Stuber E and Strober W, 1996; Yoshioka Y et al., 2000; Tsukada N et al., 2000), and OX40L-Ig fusion proteins (Higgins LM et al., 1999; Weinberg A et al., 1999). These compounds are intended either to antagonize OX40L-OX40R interaction (for preventing the accumulation of activated CD4<sup>+</sup> T cells at inflammatory sites) or to activate OX40R (as in some other pathological conditions,  
20 such as cancer).

Various OX40R binding agent, being either agonist or antagonist of OX40R, have been disclosed in the prior art as having positive effects on immunization and cancer treatment (WO 95/21915; WO 95/21251; EP 978287; WO 99/42585; WO 02/66044; US 6312700). However, only large molecule such as the OX40L whole extracellular

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AMENDMENT UNDER 37 C.F.R. § 1.111  
Patent Application  
Docket No. ARS.102



Frank C. Eisenschenk, Ph.D., Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Elly G. Stoica  
Art Unit : 1647  
Applicants : Claudio Soto-Jara, Claudia Pena-Rossi  
Serial No. : 10/510,015  
Filed : April 18, 2006  
Conf. No. : 4494  
For : OX40R Binding Agents

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action dated January 22, 2009, please amend the above-identified patent application as follows:

In the Claims

1-94 (canceled).

95. (currently amended) An isolated polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first amino acid sequence is a protein sequence other than human OX40L fused to a second amino acid sequence selected from:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said second amino acid sequence ~~polypeptide~~ contains SEQ ID NO: 13 and said fusion polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said ~~polypeptide contains contiguous amino acids of SEQ ID NO: 1~~ contain SEQ ID NO: 13 and said fusion polypeptide binds to OX40R;or
- iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a conjugate or derivative of a), b), c), d), e) or f).

96. (previously presented) The isolated polypeptide according to claim 95, wherein said fusion polypeptide or peptide comprises the amino acid sequence belonging to one or more of the following protein sequences: membrane-bound proteins, extracellular domains of membrane-bound protein, immunoglobulin constant region, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins.

97. (currently amended) The isolated polypeptide according to claim 95, ~~wherein further comprising a molecule selected from the group consisting of radioactive labels, biotin, fluorescent labels, cytotoxic agents, and drug delivery agents~~ is conjugated to a polypeptide according to claim 95a), b), c), d), e) or f).

98. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 6.

99. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

100. (currently amended) The isolated polypeptide according to claim 95, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of ~~between 5 and 10 contiguous amino acids of~~ SEQ ID NO: 1, ~~wherein said polypeptide contains~~ SEQ ID NO: 13 and binds to OX40R.

101. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 8.

102. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 13.

103. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R.

104. (currently amended) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide ~~comprising a protein sequence other than human OX40L fused to~~ and said second amino acid sequence is a peptide consisting of amino acids 94-124 of human OX40L SEQ ID NO: 6.

105. (canceled).

106. (currently amended) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence is comprising a protein sequence other than human OX40L fused to SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said fusion polypeptide or peptide ~~polypeptide~~ binds to the OX40 receptor (OX40R).

107. (currently amended) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide ~~comprising a protein sequence other than human OX40L fused to a~~ and said second amino acid sequence is a peptide consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1 that contains, ~~wherein said polypeptide contains~~ SEQ ID NO: 13 and said fusion polypeptide or peptide binds to OX40R.

108. (currently amended) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence is comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

109. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

110. (previously presented) The isolated polypeptide according to claim 95, wherein said polypeptide antagonizes the activity of OX40R.

111. (currently amended) A composition comprising a pharmaceutically acceptable carrier, excipient, stabilizer, diluent, or combination thereof and a polypeptide consisting of:

- a) ~~SEQ ID NO: 6;~~
- b) ~~SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);~~
- c) ~~between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;~~
- d) ~~SEQ ID NO: 8 or SEQ ID NO: 13;~~
- e) ~~an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;~~
- f) ~~a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:~~
  - i) ~~SEQ ID NO: 6;~~
  - ii) ~~SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);~~
  - iii) ~~between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or~~
  - iv) ~~SEQ ID NO: 8 or SEQ ID NO: 13; or~~
- g) ~~a derivative of a), b), c), d), e) or f)~~
- a) SEQ ID NO: 6;



- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first amino acid sequence is a protein sequence other than human OX40L fused to a second amino acid sequence selected from:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said second amino acid sequence contains SEQ ID NO: 13 and said fusion polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said contiguous amino acids of SEQ ID NO: 1 contain SEQ ID NO: 13 and said fusion polypeptide binds to OX40R; or
  - iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a conjugate or derivative of a), b), c), d), e) or f).

112. (previously presented) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 6.

113. (previously presented) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

114. (currently amended) The composition according to claim 111, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of ~~between 5 and 10 contiguous amino acids of~~ SEQ ID NO: 1, ~~wherein said polypeptide contains~~ SEQ ID NO: 13 and binds to OX40R.

115. (previously presented) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 8.

116. (previously presented) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 13.

117. (previously presented) The composition according to claim 111, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R and said polypeptide contains SEQ ID NO: 13.

118. (currently amended) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence comprising a protein sequence other than human OX40L fused to a peptide consisting consists of SEQ ID NO: 13.

119. (currently amended) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide ~~comprising a protein sequence other than human OX40L fused to a peptide consisting~~ and said second amino acid sequence consists of SEQ ID NO: 6.

120. (currently amended) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence comprising a protein sequence other than human OX40L fused to ~~is~~ SEQ ID NO: 6, wherein one or more amino acids have been deleted, said second amino acid sequence ~~polypeptide~~ contains SEQ ID NO: 13 and said fusion polypeptide or peptide ~~polypeptide~~ binds to the OX40 receptor (OX40R).

121. (currently amended) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence comprising a protein sequence other than human OX40L fused to a peptide consisting consists of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and said fusion polypeptide or peptide binds to OX40R.

122. (currently amended) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence consists comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

123. (previously presented) The composition according to claim 111, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

124. (currently amended) A composition of matter comprising a solid support and a polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a first amino acid sequence and a second amino acid sequence, wherein said first amino acid sequence is a protein sequence other than human OX40L fused to a second amino acid sequence selected from:

- i) SEQ ID NO: 6;
- ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said second amino acid sequence contains SEQ ID NO: 13 and said fusion polypeptide binds to the OX40 receptor (OX40R);
- iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said contiguous amino acids of SEQ ID NO: 1 contain SEQ ID NO: 13 and said fusion polypeptide binds to OX40R; or
- iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a conjugate or derivative of a), b), c), d), e) or f)
- a) ~~SEQ ID NO: 6;~~
- b) ~~SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);~~
- c) ~~between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;~~
- d) ~~SEQ ID NO: 8 or SEQ ID NO: 13;~~
- e) ~~an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;~~
- f) ~~a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:~~
  - i) ~~SEQ ID NO: 6;~~
  - ii) ~~SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);~~
  - iii) ~~between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or~~
  - iv) ~~SEQ ID NO: 8 or SEQ ID NO: 13; or~~
- g) ~~a derivative of a), b), c), d), e) or f).~~

125. (previously presented) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 6.

126. (previously presented) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

127. (currently amended) The composition of matter according to claim 124, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of ~~between 5 and 10 contiguous amino acids of~~ SEQ ID NO: 1, ~~wherein said polypeptide contains~~ SEQ ID NO: 13 and binds to OX40R.

128. (previously presented) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 8.

129. (previously presented) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 13.

130. (previously presented) The composition of matter according to claim 124, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R and said polypeptide contains SEQ ID NO: 13.

131. (currently amended) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence consists ~~comprising a protein sequence other than human OX40L fused to a peptide consisting of~~ SEQ ID NO: 6.

132. (canceled)

133. (currently amended) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence is comprising a protein sequence other than human OX40L fused to SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide second amino acid sequence contains SEQ ID NO: 13 and said fusion polypeptide or peptide binds to the OX40 receptor (OX40R).

134. (currently amended) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence comprising a protein sequence other than human OX40L fused to a peptide consisting consists of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and said fusion polypeptide or peptide binds to OX40R.

135. (currently amended) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide and said second amino acid sequence consists comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

136. (previously presented) The composition of matter according to claim 124, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

137. (previously presented) An isolated peptide, peptide mimetic, or a non-peptide mimetic of SEQ ID NO: 8 or SEQ ID NO: 13.

138. (previously presented). The isolated polypeptide according to claim 95, wherein said polypeptide is acetylated, carboxylated or PEGylated.

Remarks

Claims 95-138 are pending in the subject application. By this Amendment, Applicants have canceled claims 105 and 132 and amended claims 95, 97, 100, 104, 106-108, 111, 114, 118-122, 124, 127, 131, 133, 134, and 135. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 95-104, 106-131 and 133-138 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claim 97 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, dependent claim 97 is worded as “further comprising a molecule...” while the independent claim 95 is drawn to “an isolated peptide consisting of”. In this regard, it is noted that independent claim 95 has been amended to recite a “conjugate or derivative of a), b), c), d), e) or f)” and claim 97 corresponds to elements that can be conjugated to the peptides recited in a), b), c), d), e) or f) of claim 95. Accordingly, reconsideration and withdrawal of the objection is respectfully requested as claim 97 further limits claim 95.

Claims 95-97, 100, 104, 106, 107, 109, 110, 111, 113-114, 120, 121, 123, 124, 126-127, 133, 134, 136, and 138 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates that the words “said polypeptide” are unclear in claims 95, 111 and 124, the phrase “wherein said polypeptide consists of between 5 and 10 contiguous amino acids of between 5 and 10 contiguous amino acids of SEQ ID NO: 1” is unclear in claims 100, 114, and 127, and the phrase “fused to a peptide consisting of amino acids 94-124 of human OX40L” is indefinite in claim 104. Applicants have amended the claims in an effort to attend to these issues and request the courtesy of an interview to discuss any additional issues the Examiner may identify when considering these amendments. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claim 138 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed

invention. The Office Action indicates that the specification does not disclose that the peptide is PEGylated. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. For example, page 16, lines 5-10 of the as-filed specification clearly discusses conjugates or complexes of the claimed peptides, including conjugates containing polyethylene glycol. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 95-97, 99-100, 102-104, 106-111, 113-114, 116-118, 120-124, 126-127, 129-130 and 133 -138 are rejected under 35 U.S.C. 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for isolated peptides, compositions containing them, comprising SEQ ID NOs: 6 and 8 but is not enabled for SEQ ID NO: 13. Applicants respectfully assert that the claims as filed are enabled.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention (*Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 U.S.P.Q. 592, 599 (Fed. Cir. 1983)) and is not precluded even if some experimentation is necessary. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Applicants also submit that nothing more than objective enablement is required, and therefore, it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Additionally, the Patent and Trademark Office Board of Patent Appeals and Interferences has stated: "The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed". *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982); *see also Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result).



In this case, the as-filed specification provides adequate teaching with respect to screening assays (see, for example, pages 25-26 and Examples 1-2). The as-filed specification also provides the peptide to be tested in such assays. While testing the claimed peptide for its ability to bind to the OX40R may be laborious and/or tedious, such experimentation would not constitute undue experimentation since one was using known methods and a disclosed peptide to ascertain its ability to bind OX40R. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 95-136 are rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991) and Hamaoui *et al.* (1990). The Office Action indicates that Godfrey *et al.* teach purified ACT-4-L ligand polypeptides, an exemplified ACT-4-L ligand designated ACT-4-L-h-1. Chien *et al.* is cited as teaching a method by which a protein-protein interaction is identified in vivo through reconstitution of the activity of a transcriptional activator. Applicants respectfully assert that the claimed invention is not obvious over the cited references and note that the Office Action of January 22, 2009 indicates that the previously submitted arguments have been carefully considered but not found persuasive since the two-hybrid system of Chien *et al.* would have easily identified a binding motif.

Applicants submit that the current rejection is based upon improper hindsight reconstruction of the claimed invention. While Applicants recognize that such a reconstruction of the invention is proper so long as an obviousness rejection takes into account only the knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicants' disclosure (*In re McLaughlin*, 443 F.2d 1392, 1395, 170 U.S.P.Q. 209, 212 (C.C.P.A. 1971)), it is respectfully submitted that Applicants' disclosure has been used to serve as the basis of the rejection currently of record.

Applicants submit that the current finding of obviousness for the claimed invention is based upon the impermissible use of the data and knowledge gleaned from the as-filed specification. As noted previously, the as-filed specification indicates (at page 2) that:

OX40L interacts with OX40R as a homotrimer with a high affinity ( $K_d = 0.2$ - $0.4$  nM), and various binding assays have been tested on this system (Taylor L *et al.*, 2002; Taylor L and Schwartz H, 2001; Al-Shamkhani A *et al.*, 1997). However, no tridimensional structure has been solved so far, neither detailed structure-activity

studies have been performed, in order to provide any further molecular details on the mechanism of OX40L-OX40R interaction.

Thus, the as-filed specification indicates that it is unknown whether OX40L interacts with its cognate receptor via a linear peptide or via a conformational arrangement of the homotrimer and the cited combination of references provides no teaching as to why one of skill in the art, in view of such a recognition, would, **absent the teachings of the as-filed specification**, have had a reasonable expectation of identifying linear peptides having the ability to bind to OX40R and antagonize its activity.

Applicants further note that only large molecules, such as the extracellular domain of OX40L or antibodies that bind to OX40R, were recognized in the art as being effective OX40R binding agents (see paragraph bridging pages 3-4 of the as-filed specification) and that the majority of these agents were recognized to be agonists of OX40R. Thus, **absent the teachings of the as-filed specification**, one skilled in the art would not have expected small linear peptides would have had the ability to bind to OX40R and antagonize the activity of the receptor and/or its interaction with OX40L. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 137 is rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991) and Hruby *et al.* (2000). The Office Action states that Hruby *et al.* teach the design of peptidomimetic ligands with agonist biological activities. Applicants respectfully assert that the claimed invention is not obvious over the cited references and that the addition of Hruby *et al.* does nothing to cure the issues noted above with respect to the combined teachings of Godfrey *et al.* and Chien *et al.* Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claim 138 is rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991) and Quillan *et al.* (U.S. Patent No. 6,602,856). The Office Action notes that Quillan *et al.* teach peptide antagonists of  $\alpha$ -melanocyte stimulating hormone. Applicants respectfully assert that the claimed invention is not obvious over the cited references and that the addition of Quillan *et al.* does nothing to cure the issues noted above with

respect to the combined teachings of Godfrey *et al.* and Chien *et al.* Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.

Patent Attorney

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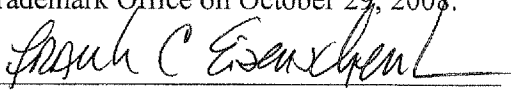
Gainesville, FL 32614-2950

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I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on October 29, 2008.

AMENDMENT UNDER 37 C.F.R. § 1.114  
Patent Application  
Docket No. ARS.102



Frank C. Eisenschenk, Ph.D., Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Elly Gerald Stoica  
Art Unit : 1647  
Applicants : Claudio Soto-Jara, Claudia Pena-Rossi  
Serial No. : 10/510,015  
Filed : September 30, 2004  
Conf. No. : 4494  
For : OX40R Binding Agents

Mail Stop RCE  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.114

Sir:

Applicants request that the period for response be extended three months through and including October 29, 2008, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated April 29, 2008, please amend the above-identified patent application as follows:

In the Claims

1-94. (canceled)

95. (new) An isolated polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or
  - iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a derivative of a), b), c), d), e) or f).

96. (new) The isolated polypeptide according to claim 95, wherein said fusion polypeptide or peptide comprises the amino acid sequence belonging to one or more of the following protein sequences: membrane-bound proteins, extracellular domains of membrane-bound protein,

immunoglobulin constant region, multimerization domains, extracellular proteins, signal peptide-containing proteins, export signal-containing proteins.

97. (new) The isolated polypeptide according to claim 95, further comprising a molecule selected from the group consisting of radioactive labels, biotin, fluorescent labels, cytotoxic agents, and drug delivery agents.

98. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 6.

99. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

100. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

101. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 8.

102. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of SEQ ID NO: 13.

103. (new) The isolated polypeptide according to claim 95, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R.

104. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of amino acids 94-124 of human OX40L.

105. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 6.

106. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

107. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

108. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

109. (new) The isolated polypeptide according to claim 95, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

110. (new) The isolated polypeptide according to claim 95, wherein said polypeptide antagonizes the activity of OX40R.

111. (new) A composition comprising a pharmaceutically acceptable carrier, excipient, stabilizer, diluent, or combination thereof and a polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or
  - iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a derivative of a), b), c), d), e) or f).

112. (new) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 6.

113. (new) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).



114. (new) The composition according to claim 111, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

115. (new) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 8.

116. (new) The composition according to claim 111, wherein said polypeptide consists of SEQ ID NO: 13.

117. (new) The composition according to claim 111, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R and said polypeptide contains SEQ ID NO: 13.

118. (new) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 13.

119. (new) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 6.

120. (new) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

121. (new) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide

consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

122. (new) The composition according to claim 111, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

123. (new) The composition according to claim 111, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

124. (new) A composition of matter comprising a solid support and a polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or

- iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a derivative of a), b), c), d), e) or f).

125. (new) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 6.

126. (new) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

127. (new) The composition of matter according to claim 124, wherein said polypeptide consists of between 5 and 10 contiguous amino acids of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

128. (new) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 8.

129. (new) The composition of matter according to claim 124, wherein said polypeptide consists of SEQ ID NO: 13.

130. (new) The composition of matter according to claim 124, wherein said polypeptide consists of an active mutant of a), b), c) or d), wherein three or fewer amino acids are conservatively substituted and said active mutant binds to OX40R and said polypeptide contains SEQ ID NO: 13.

131. (new) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 6.

132. (new) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 6.

133. (new) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R).

134. (new) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R.

135. (new) The composition of matter according to claim 124, wherein said polypeptide is a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to a peptide consisting of SEQ ID NO: 8 or SEQ ID NO: 13.

136. (new) The composition of matter according to claim 124, wherein said polypeptide is a derivative of a), b), c), d), e) or f).

137. (new) An isolated peptide, peptide mimetic, or a non-peptide mimetic of SEQ ID NO: 8 or SEQ ID NO: 13.

138. (new). The isolated polypeptide according to claim 95, wherein said polypeptide is acetylated, carboxylated or PEGylated.

Remarks

Claims 35-37, 39 and 57-94 are pending in the subject application. By this Amendment, Applicants have canceled claims 35-37, 39 and 57-94 and added new claims 95-138. Support for the new claims can be found throughout the subject specification and in the claims as originally filed and previously presented (the claims have been revised to indicate SEQ ID NOs: for the peptides previously claimed and pages 14-16 of the as-filed specification). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 95-138 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that the previous After Final amendment was not entered in this matter. Entry of the amendments and arguments presented therein is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that previously submitted arguments were not found persuasive and states that adequate written description is conferred by correlation between structure and function. The Office Action further argues that the claims are drawn to a genus of polypeptides that are defined by their functionality and that fusion proteins, active mutants and peptides of between 5 and 10 amino acids that bind OX40R do not have adequate written description. While the rejection is now moot in view of the cancellation of claims 35-37, 39 and 57-94, Applicants traverse the rejection as it may be applied to the newly presented claims.

At the outset, Applicants note that each of the polypeptides that are alleged to lack adequate written description are defined by both structure and function within the claims. For example, claim 95 recites:

An isolated polypeptide consisting of:

- a) SEQ ID NO: 6;
- b) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);

- c) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R;
- d) SEQ ID NO: 8 or SEQ ID NO: 13;
- e) an active mutant of a), b), c) or d), wherein one or more of the amino acids has been conservatively substituted and said active mutant binds to OX40R;
- f) a fusion polypeptide or peptide comprising a protein sequence other than human OX40L fused to:
  - i) SEQ ID NO: 6;
  - ii) SEQ ID NO: 6, wherein one or more amino acids have been deleted, said polypeptide contains SEQ ID NO: 13 and said polypeptide binds to the OX40 receptor (OX40R);
  - iii) between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R; or
  - iv) SEQ ID NO: 8 or SEQ ID NO: 13; or
- g) a derivative of a), b), c), d), e) or f).

As will be noted from the claims, each of the claim subparts recite peptides that have structural limitations or both structural and functional limitations. For example, subpart c) recites a peptide consisting of between 5 and 10 contiguous amino acids of SEQ ID NO: 1, wherein said polypeptide contains SEQ ID NO: 13 and binds to OX40R. Thus, it is respectfully submitted that adequate written description of such a peptide exists in the as-filed specification. Likewise, fusion proteins containing such a peptide also have adequate written description.

With respect to derivatives of the claimed polypeptides, it is respectfully submitted that these peptides are adequately described. For example, derivatives are defined at page 14 and refer “to derivatives which can be prepared from the functional groups present on the lateral chains of the amino acid moieties or on the N-/ or C-terminal groups according to known methods. Such derivatives include for example esters or aliphatic amides of the carboxyl-groups and N-acyl derivatives of free amino groups or O-acyl derivatives of free hydroxyl-groups and are formed with

acyl-groups as for example alcanoyl- or aroyl-groups". Thus, it is respectfully submitted that the as-filed specification and claims conform to the written description requirement of section 112.

Finally, the Office Action argues that active mutants of the claimed polypeptides are not supported by the as-filed specification. In this regard, Applicants respectfully traverse. The as-filed specification indicates that the OX40R binding portion of the disclosed peptides is associated with amino acids 107-111 of SEQ ID NO: 13 (see Example 2, page 36, lines 11-15 and Figure 6). Further, the as-filed specification discloses a number of peptides having the recited characteristics (see Example 2) and the as-filed specification (at pages 9-10) provides teaching as to substitutions that can be made within the claimed peptides and methods of screening the peptides for activity (OX40R binding). Applicants also note that the term "active" is defined in the as-filed specification as a compound demonstrating the OX40R binding properties of the peptides disclosed within the as-filed application (see page 9, lines 9-10). Applicants further note that the claims indicate that the active mutants of the claimed polypeptides must also bind to OX40R and that the amino acid substitutions are to be made are also specified. Thus, it is respectfully submitted that the claimed polypeptides are defined both structurally and functionally and that adequate written description of the claimed polypeptides was provided in the as-filed specification. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action argues that it is unclear as to whether the phrase "one or more" may include a situation in which all the amino acids may be substituted. Applicants respectfully submit that the claims are definite and that one skilled in the art, in view of the teachings of the as-filed specification, would be able to ascertain the metes and bounds of the claimed invention (see, for example, page 9, lines 11-17). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 35-37, 39 and 57-94 are rejected under 35 U.S.C. § 103(a) as obvious over Godfrey *et al.* (U.S. Patent No. 6,242,566) in view of Chien *et al.* (1991). The Office Action asserts that Godfrey *et al.* teach purified ACT-4-L ligand polypeptides; an exemplified ACT-4-L ligand designated ACT-4-l-h-1. In addition, it is stated that Godfrey *et al.* teach purified extracellular domains of ACT-4-L ligands. The Office Action cites Chien *et al.* as teaching a method by which a

protein-protein interaction is identified in vivo through reconstitution of the activity of a transcriptional activator. Applicants note that the Office Action also asserts that the claimed invention is obvious and that one skilled in the art would have arrived at the domains essential to the binding of ACT 4L to its receptor because the domain to be searched was disclosed by Godfrey *et al.*, the search would have entailed a finite number of fragments already envisioned (in length). Applicants respectfully traverse the rejection and submit that a *prima facie* case of obviousness has not been established by the Patent Office.

At the outset, Applicants note that the obviousness rejection of record appears to rely on the rationale articulated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) in establishing the rejection of record. Applicants also note that the Patent Office's guidelines promulgated in light of the KSR decision also provide a similar rationale for establishing an obviousness rejection (see 72 Fed. Reg. 57526, 57532). Applicants further note that the full quote of that portion of the KSR decision which appears to serve as the basis of the instant rejection states that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." Further, the Patent Office guidelines state (at page 57532):

E. "Obvious To Try"—Choosing From a Finite Number of Identified, Predictable Solutions, With a Reasonable Expectation of Success

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and



(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

In this case, Applicants respectfully submit that the Patent Office has failed to establish the *prima facie* obviousness of the claimed invention as the rejection of record fails to meet the requirements of either the KSR decision or the guidelines promulgated by the Patent Office. Namely, the Patent Office has failed to establish that there was a recognized problem or need in the art to solve a problem that would have motivated one to even try to identify peptides corresponding to those claimed in this matter. Further, the Patent Office has failed to establish that there were a finite number of identified, predictable solutions for solving the recognized need or problem. It is noted that the Office Action argues that there are a finite number of peptide fragments that can be generated in light of the teachings of Godfrey *et al.*; however, it is clear that thousands or tens of thousands of possible fragments could be generated from the 133 amino acid extracellular domain of the OX40L and no finding as to which of those fragments would have predictably solved the problem (which is, as of yet, unidentified by the Patent Office) has been made.

It is further submitted that a *prima facie* case of obviousness has not been established as it is unclear that one skilled in the art would have had a reasonable expectation of success in arriving at the claimed invention on the basis of the cited references. For example, the as-filed specification indicates (at page 2) that:

OX40L interacts with OX40R as a homotrimer with a high affinity ( $K_d = 0.2\text{-}0.4$  nM), and various binding assays have been tested on this system (Taylor L et al, 2002; Taylor L and Schwartz H, 2001; Al-Shamkhani A et al., 1997). However, no tridimensional structure has been solved so far, neither detailed structure-activity studies have been performed, in order to provide any further molecular details on the mechanism of OX40L-OX40R interaction.

Thus, the as-filed specification indicates that it is unknown whether OX40L interacts with its cognate receptor via a linear peptide or via a conformational arrangement of the homotrimer and the cited combination of references provides no teaching as to why one of skill in the art, in view of such a recognition, would have had a reasonable expectation of identifying linear peptides having the ability to bind to OX40R and antagonize its activity.

Applicants further note that only large molecules, such as the extracellular domain of OX40L or antibodies that bind to OX40R were recognized in the art as being effective OX40R binding agents (see paragraph bridging pages 3-4 of the as-filed specification) and that the majority of these agents were recognized to be agonists of OX40R. This recognition, too, would not have led one skilled in the art to expect that small linear peptides would have had the ability to bind to OX40R and antagonize the activity of the receptor and/or its interaction with OX40L.

Additionally, the claimed peptides exhibit a greater ability to inhibit (antagonize) the interaction between OX40L and OX40R as compared to a control (using the AlphaScreen technology described in Example 1). In this regard, Applicants attach a comparative table demonstrating that all peptides within the extracellular domain of OX40L did not exhibit a higher affinity to OX40R in the AlphaScreen Assays presented in Example 2. The data in this table is found throughout the as-filed specification (support for the binding tests results now provided in tabular form can be found in the as-filed specification as indicated in the last three columns of the Table). As is apparent from the Table, only the claimed peptides, all sharing the core amino acid sequence of SEQ ID NO: 13, exhibit the ability to act as OX40L antagonists and block the interaction of OX40L with OX40R. Accordingly reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established in this matter.

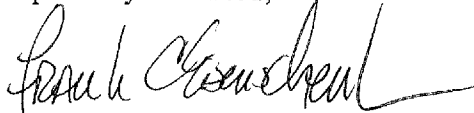
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl

Attachment: Comparative Table

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,758,852

Page 1 of 1

APPLICATION NO.: 10/510,015

DATED : July 20, 2010

INVENTORS : Claudio Soto-Jara, Claudia Pena-Rossi

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2,

Line 19, "CD4 T cells" should read --CD4<sup>+</sup> T cells--.

Column 29,

Line 51, "a SEQ ID NO: 6;" should read --a) SEQ ID NO: 6; --.

Line 53, "deleted said" should read --deleted, said--.

Column 30,

Line 10, "iv SEQ ID NO:" should read --iv) SEQ ID NO: --.

Line 40, "frision polypeptide" should read --fusion polypeptide--.

MAILING ADDRESS OF SENDER:

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